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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,159	JANJIC ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/03, 10/04, 12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group II, claims 7 and 8, in the reply filed on February 16, 2006 is acknowledged.

Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 16, 2006.

Specification

The disclosure is objected to because of the following informalities: the specification contains symbols whose meaning is unknown. See for example page 8, line 29 and page 63, line 2. An exhaustive search of the specification has not been done and there may be other instances of symbols of unknown meaning.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 7 is directed to a method of improving the pharmacokinetic properties of a PDGF nucleic acid ligand by covalently linking the ligand to either a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient. Claim 8 is directed to a method of targeting a therapeutic or diagnostic agent to a particular predetermined biological target in a patient by covalently linking the agent to a complex of a PDGF nucleic acid ligand and a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient.

The claimed invention is directed to improving the pharmacokinetic properties and drug delivery ability of a nucleic acid ligand by conjugating the ligand to a compound that is a high molecular weight non-immunogenic compound and administering the complex to a patient. The specification defines the phrase non-immunogenic, high molecular weight compound as being any compound 1000 Da or more that typically does not generate an immunogenic response and recites polyethylene glycol, polysaccharides, polypeptides, magnetic structures and even other nucleic acid ligands as examples of such compounds.

The compounds contemplated as being usable in the claimed method constitute a large genus of compounds. The specification provides some general guidance of what would be included in this genus, but there is no structure demonstrated in the specification or known in the art to correspond to the function of being a non-

immunogenic, high molecular weight compound. Polyethylene glycol is recited as an example of a non-immunogenic high molecular weight compound and the working examples in the specification exemplify its use in conjugates of PDGF nucleic acid ligands, but the structure of PEG does not lead the skilled artisan to the structure of other compounds such as polysaccharide or magnetic structures that would be non-immunogenic. Polypeptides such as albumin are also contemplated as being non-immunogenic high molecular weight compounds but it is unknown what structure within albumin confers the function of being non-immunogenic such that the skilled artisan would be able to recognize that another protein is or is not immunogenic.

Claim 8 is directed to a method of targeting a therapeutic or diagnostic agent to a specific predetermined biological target that is expressing PDGF in a patient. The specification contemplates that the use of nucleic acid ligands to deliver therapeutic agents is part of the invention but doesn't describe how the site of delivery is predetermined. The specification also does not describe if the specific predetermined target is meant to be the exclusive place of delivery. The specification provides examples wherein PDGF nucleic acid ligands are active agents but does not provide any examples of delivery of a therapeutic agent covalently linked to a nucleic acid ligand complex to a target within a patient. It is unclear if performing the method of claim 8 requires additional unclaimed steps of predetermining where the ligand will be targeted in a patient.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is,

for purposes of the 'written description' inquiry, whatever is now claimed. The skilled artisan cannot envision the detailed structure of the encompassed non-immunogenic high molecular weight compounds, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. (US 5,270,163, cited on IDS) in view of Tullis (WO 88/09810, cited on IDS) and Ferns et al. (Science 1991, vol. 253, pages 1129-1132).

Claim 7 is directed to a method of improving the pharmacokinetic properties of a PDGF nucleic acid ligand by covalently linking the ligand to either a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient. Claim 8 is directed to a method of targeting a therapeutic or diagnostic agent to a particular predetermined biological target in a patient by covalently linking the agent to a complex of a PDGF nucleic acid ligand and a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands include growth factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to a non-immunogenic, high molecular weight compound or a lipophilic compound.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic and imparts amphiphilic character to the final product. At page 7 solubility modifying moieties are taught as including

polyethylene glycol as well as lipophilic compounds such as palmitate, distearylglyceride and cholesteryl. Tullis teaches that the conjugates of the invention find use in therapeutics wherein the amphiphilic nature of the conjugate aids in transport across the cellular membrane.

Ferns et al. teach that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis after angioplasty. Ferns et al. further teach that administration of PDGF antibodies to rats before and after balloon catheter deendothelialization, a model of angioplasty induced restenosis, reduced the amount of smooth muscle cell accumulation observed. Ferns et al. teach that their findings suggest possible approaches for prevention of restenosis following angioplasty.

It would have been obvious to one of ordinary skill in the art at the time of invention to improve the pharmacokinetic properties of a nucleic acid ligand as taught by Gold et al. by conjugating the ligand to a solubility modifying moiety such as PEG or cholesterol as taught by Tullis. It would have been further obvious to one of ordinary skill to make nucleic acid ligands that are targeted to PDGF. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties, teaching that such conjugates are transported across cellular membrane and are more effective at inhibiting gene expression. It would have further been obvious to use a nucleic acid ligand complex to deliver a therapeutic or diagnostic agent. Gold et al. provide a motivation to use a nucleic acid ligand to deliver a therapeutic agent, specifically reciting that drug delivery vehicles are one of the utilities of nucleic acid ligands. Ferns et al. provide a motivation to target PDGF, teaching that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis and that

inhibition of PDGF reduces restenosis. One of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to PDGF because Gold et al. teach a method of isolating nucleic acid ligands to any target molecule and state that growth factors are a desired target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates can be made using routine synthesis methods.

Thus, the invention of claims 7 and 8 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
April 24, 2006

Director, TC 1600

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER